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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/091,300	03/04/2002	Patricia Rockwell	11245/46211	1694

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EXAMINER
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BLANCHARD, DAVID J

ART UNIT	PAPER NUMBER
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1643

DATE MAILED: 08/04/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

**Office Action Summary**

Application No.

10/091,300

Applicant(s)

ROCKWELL ET AL.

Examiner

David J. Blanchard

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 19 May 2006.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-6,9,11-14,16-18,28,62 and 67-69 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-6,9,11-14,16-18,28,62 and 67-69 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)  
Paper No(s)/Mail Date \_\_\_\_\_
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date. \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: \_\_\_\_\_

### **DETAILED ACTION**

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 19 May 2006 has been entered.
2. Claims 7-8, 10, 15, 19-27, 29-61 and 63-66 are cancelled.
3. Claims 1-6, 9, 11-14, 16-18, 28, 62 and 67-69 are pending and under examination.
3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

### ***Response to Arguments***

4. The rejection of claims 1-6, 9, 11-14, 16-18, 28, 62 and 67-69 under 35 U.S.C 103(a) as being unpatentable over Rockwell et al (Molecular and Cellular Differentiation. 3(4): 315-335, 1995, Ids filed 6/18/2003) in view of Ciardiello et al (Clinical Cancer Research, 6:3739-3747, September 2000, cited previously on PTO-892 mailed 3/30/05) and Siemeister et al (Cancer and Metastasis Reviews 17: 241-248, 1998, cited previously on PTO-892 mailed 12/22/03) and Thorpe et al (US Patent 6,342,219 B1, 4/28/1999, IDS filed 2/9/04) is maintained.

The response filed 5/19/2006 argues that one skilled in the art would not be motivated to substitute the VEGF antisense described by Ciardiello with a VEGFR antibody as described by Rockwell for the following reasons. First, Ciardiello describes preventing and eliminating VEGF entirely using a VEGF antisense oligonucleotide, whereas Rockwell describes inhibiting VEGF further downstream, i.e., inhibiting the interaction between VEGF and VEGF receptors to inhibit angiogenesis, referencing Fig. 4. Applicant states that VEGF mediates its regulatory response on endothelial cells through two high affinity PRK receptors, mouse flk-1 and its human homolog KDR/flk-1 and a second receptor, flt-1 (see pg. 321). Thus, applicant concludes that one skilled in the art would not be motivated to use VEGFR antibodies instead of VEGF antisense because antibodies to both flk-1 and flt-1 may be required to get the same results as with VEGF antisense. This has been fully considered, but is not found persuasive. As stated in the rejection, Rockwell teaches that DC101 (anti-VEGFR antibody) cross-reacts with both human VEGFR receptor forms, flt-1 and KDR and was shown to block VEGF receptor mediated activation in tumor cells. Further, applicant presumes that a single VEGF antisense oligonucleotide would be sufficient, where it is known that there are many different isoforms of VEGF (see pg. 31 2<sup>nd</sup> col. of Miao et al supplied by applicant 4/13/2006).

Applicant also argues that as of the filing date of the present application, it was known that neuropilin-1, which binds to VEGF, also mediates angiogenesis via its interaction with VEGF, referring to Exhibit A, submitted in the response filed 4/13/2006. According to applicant binding of VEGF to three different receptors may need to be

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blocked in order to get the same result as a single VEGF antisense. It is applicants' position that such a multi-receptor approach undercuts any motivation to replace the VEGF antisense described by Ciardiello with a VEGF antibody described by Rockwell. This has been fully considered but is not found persuasive. Exhibit A, or more specifically, the art of Miao et al (Cancer and Metastasis Reviews, 19:29-37, 2000) and Soker et al (Cell, 92:735-745, March 20, 1998) with which applicant argues teach that there are many VEGF isoforms, VEGF<sub>121</sub> and VEGF<sub>165</sub> being the most abundant isoforms and neuropilin-1 binds VEGF<sub>165</sub>, but not VEGF<sub>121</sub> (Soker et al, abstract and pg. 735, 2<sup>nd</sup> col. and Miao et al pg. 31, 2<sup>nd</sup> col. and pg. 32, 1<sup>st</sup> col.). Further, Miao et al teach that endothelial cells expressing neuropilin-1 alone did not respond to either VEGF isoform, indicating that neuropilin-1 was not a signaling receptor for chemotaxis (see pg. 32, 1<sup>st</sup> col.). However, the co-expression of VEGFR-2 and neuropilin-1 in endothelial cells enhanced VEGF<sub>165</sub> binding to VEGFR-2 and VEGF<sub>165</sub> mediated chemotaxis compared to endothelial cells expressing VEGFR-2 alone, suggesting that neuropilin-1 acts as a co-receptor for VEGFR-2 (see pg. 32, 1<sup>st</sup> col. and Fig. 2). Therefore, given that neuropilin-1 does not independently bind VEGF and mediate angiogenesis, but acts as a co-receptor to enhance VEGFR-2 mediated activity (particularly Fig. 2 of Miao et al) and in view of the teachings of Rockwell, that monoclonal antibody DC101 cross-reacts with both human VEGF receptors (flk-1 andflt-1), blocking VEGF ligand binding with monoclonal antibody DC101 would inhibit all three receptors.

Applicant further states that Ciardiello mentions that antibodies against VEGF-specific flk-1/KDR is "a promising approach" and although Cardiello recognizes the use of antibodies, which would target VEGF after VEGF is produced, Ciardiello pursues a dual approach to reducing VEGF from even being produced by tumor cells comprising VEGF antisense and C225 (anti-EGFR antibody). Rockwell on the other hand describes antibodies that bind VEGFR and inhibit binding of VEGF to its receptor and that do not target the production of VEGF. This has been fully considered but is not found persuasive. Applicant is reminded that "[t]he prior art's mere disclosure of more than one alternative does not constitute a teaching away from any of these alternatives because such disclosure does not criticize, discredit, or otherwise discourage the solution claimed..." In re Fulton, 391 F.3d 1195, 1201, 73 USPQ2d 1141, 1146 (Fed. Cir. 2004). In fact, as pointed out by applicant Cardiello et al mentions that antibodies against the VEGF-specific flk-1/KDR is "a promising approach". The following is reiterated for applicants' convenience. Rockwell teaches that blocking or inhibiting ligand binding to the EGFR with an anti-EGFR antibody (monoclonal antibody 225 and C225 (chimeric version of antibody 225, also known as Erbitux®) inhibits tumor growth and blocking or inhibiting ligand binding to the VEGFR with monoclonal antibody DC101 also inhibits tumor growth, which when considered in view of the teachings of Ciardiello, indicating that when the ligands for both EGFR and VEGFR are blocked or inhibited, the combination produces a synergistic tumor growth inhibitory effect. Thus, there is a clear suggestion that there would be an advantage to combining the anti-EGFR antibody with the anti-VEGFR antibody to achieve a synergistic tumor inhibitory effect that

significantly improves survival and almost complete suppression of tumor growth, whereas inhibition of ligand binding to EGFR alone or inhibition of ligand binding to VEGFR alone results in cytostatic and reversible growth-inhibitory effect according to Ciardiello. Applicant is reminded that the strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. *In re Sernaker*, 702 F.2d 989, 994-95, 217 USPQ 1, 5-6 (Fed. Cir. 1983) (see MPEP 2144).

For these reasons and those already of record the rejection is maintained.

### ***Conclusions***

5. No claim is allowed.

6. This is a continued examination of applicant's earlier Application. All claims are drawn to the same invention claimed in the earlier application and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the earlier application. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action in this case. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not

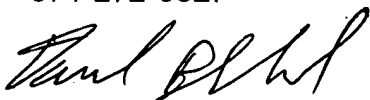
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mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however, event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571) 272-0827. The examiner can normally be reached at Monday through Friday from 8:00 AM to 6:00 PM, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached at (571) 272-0832. The official fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,  
David J. Blanchard  
571-272-0827



LARRY R. HELMS, PH.D.  
SUPERVISORY PATENT EXAMINER